

# Safety reporting in clinical trials: there's no time to wait

With the intense focus on drug safety by the public, press and political entities, sponsors should separate the time-sensitive process of suspected unexpected serious adverse reaction reporting from the long-term process of clinical data management, argue **Ralph E Bobo, MD**, Executive Vice President of the Pharmacovigilance Practice at Sentrx, and **Jill M Notte**, Sentrx's Director of Marketing.

**B**y design, clinical trials generate high volumes of data. Without data, statistically significant results could not be obtained. In a traditional study, hundreds of investigators complete multi-page paper case report forms (CRFs) for thousands of patients. CRF data is then keyed into the clinical data management system (CDMS) twice and validated for accuracy, a process known as double-data entry. Information from a patient visit may not be available in the system for weeks, but the delay is only significant at the end of the trial as the effort begins to secure the data and analyze the results.

Electronic data capture (EDC) solutions have the potential to revolutionize clinical data management. Investigators enter information from patient visits directly into the CDMS through an electronic form with standardized choices and error-checking protocols, eliminating double-data entry from often-illegible paper CRFs. Numerous case studies have been presented on the benefits EDC delivers with respect to time, productivity and costs. However, one aspect of clinical trials that EDC solutions have not adequately addressed is the processing of seri-

Table 1: Diverging characteristics of efficacy and safety – Copyright Sentrx, 2003

Clinical data management	SUSAR reporting
Defined end point	Spontaneous
Big # statistics	Small # statistics
Structured data	Unstructured data
Results	Events
Data management	Medical knowledge
Expected	Unexpected
Benefit	Risk
Mass dependent	Individual dependent
Duration of months	Duration of days

ous adverse events (SAEs) – specifically, suspected unexpected serious adverse reactions (SUSARs).

SUSAR reporting to regulatory authorities is very different from clinical data management, as shown in Table 1. It is a time-sensitive process, driven by regulations and guidelines from countries, regions, standards organizations, oversight committees and company practices. It requires the immediate attention of healthcare professionals adhering to standard operating procedures (SOPs) and good clinical practices (GCPs). From an information technology perspective, SUSAR reporting requires transaction-based processing, rather than batch data transfer at scheduled intervals. Sponsors cannot rely on the relatively long-term

process of clinical data management to meet deadlines as short as seven calendar days for notifying regulators of SUSARs.

## The critical difference between safety and efficacy

Those unfamiliar with the challenges of drug safety may believe that implementing EDC solutions will improve the SAE process. They may consider an

electronic SAE intake form to be simply a specialized eCRF designed to capture the information required for regulatory reporting; or that the same query management processes and tools used to address incomplete or inconsistent efficacy data can be applied to safety data. This belief is not accurate.

When an SAE is reported, rapid communication between sponsor and investigator is required. Medical opinions on causality and expectedness must be agreed upon, affecting whether regulatory authorities need to be notified within timelines as short as seven calendar days. In a SUSAR case, regulatory guidelines recommend the unblinding of the patient's study medication to help oversight committees determine if it is ethical for the trial to continue; and blinding data ideally should be hidden from the clinical



## THE SAE REPORTING PROCESS

Sentrx divides the process of adverse event reporting in development and post-marketing into four steps: intake, investigation, integrity and reporting.

In clinical trials, intake involves receiving information regarding an SAE from the investigator site and confirming receipt. This is typically done by fax, but can also be done electronically or by phone. The goal of this step is to obtain as much information as possible while the event is still fresh to all involved. The initial data collected is entered into the safety database. A well-designed Intake process reduces the number of subsequent queries, allows an event to be classified appropriately and speeds regulatory reporting.

Investigation includes querying the site for missing information, clarifying data that is illegible or inconsistent, and obtaining documentation such as lab reports, hospital records and death reports. During the query process, a qualified healthcare professional communicates with the investigator and other entities via fax, phone, encrypted e-mail or secure web-based methods. Being persistent and expeditious in the investigation effort is critical in determining if the event must be classified as serious, unexpected and causally related to the study drug and thus requires an alert report to regulatory authorities and investigators. The case continues to be updated in the safety system as the drugs involved, symptoms, diagnosis, medical history and laboratory data are coded against standard medical dictionaries, such as the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization (WHO) Drug Dictionary. A narrative presentation of the data is written by a healthcare professional to put the parameters of the case into the proper context.

Integrity occurs as the regulatory report is generated and the case is reviewed for quality. A medical doctor ensures that the diagnosis is plausible; the event is coded properly; the classification of the event as it relates to seriousness, expectedness and causality is appropriate; and the narrative is a complete and accurate description of the case.

Reporting is the act of submitting the case to all appropriate regulatory authorities and ethics committees by the sponsor and investigator within the mandatory timeframe and in the required format, such as the US Food and Drug Administration's (FDA) MedWatch Form 3500A or the Council for International Organizations of Medical Sciences (CIOMS) I form. European regulatory authorities now require SUSAR reports to be submitted electronically in a standard XML file schema called E2BM.

analysis team to avoid bias. To date, the EDC industry has not addressed the urgency and complexity of SUSAR reporting. Improvements must be sought with process change and interim technology until these solutions mature.

### The centralized SAE process

Although the use of EDC is expanding, most trials are still paper-based. Sponsors often engage more than one CRO, each employing a different set of technologies. Many trials involve hundreds of investigators with varying degrees of sophistication. In turn, sites involved in multiple trials may be asked to use

several different systems. The lack of consistency in processes and systems can lead to SAEs being assessed incorrectly, reported late or missed entirely.

No matter the diversity of vendor or technology solutions employed, sponsors should have one centralized process for SAE reporting outside of clinical data management. All SAEs should be entered into the company safety system within 24 hours of receipt. The query process should be deliberate, with consistent scheduling of interactions between sites and well-trained safety monitors. Fax, phone, encrypted e-mail, and secure web methods should all be offered as options for communication.

***“SAEs cannot simply be treated as additional data points, as SUSARs have the potential to stop a trial, render a drug unapprovable, or trigger the requirement of a risk management program”***

### The movement toward SAE centralization

Companies in the biopharmaceutical industry are beginning to see the need to separate the safety and efficacy processes. Sentrx began supporting this effort in 2001 for a large global pharmaceutical company, which had grown steadily through a series of significant acquisitions. SAEs were being reported in a variety of formats to many departments, depending on the study drug and site location. By centralizing SAE reporting, the company reduced the number of queries from 4-7 per case to 2-3 per case, reduced the average age of queries from several months to less than five days, and ensured timely regulatory reporting.

Another benefit the firm realized was an improved ability to rank investigators. For instance, some sites had high patient recruitment rates but consistently provided poor quality data and generated many queries per SAE. With these performance metrics identified and quantified, the company gained insight into cost drivers and refined their site selection criteria.

Smaller companies are also seeking to improve their SAE reporting process. One mid-sized biopharmaceutical company realized that, as it operated multiple trials using three CROs, its safety data was decentralized and it had no control over the variability between each vendor's processes. The company chose to remove the responsibility of handling SAEs from all CROs and instituted a specialized process, system and vendor. In another example, a small pharmaceutical company was starting a trial with 200 sites in the US and Europe, using a mix of contracted and in-house clinical research associates (CRAs) for monitoring. Although the entire trial was to be operated using EDC, the company understood the unique and critical requirements of SAE reporting and separated that process from the clinical data management function.

### Applying technology to a centralized process

To support SAE centralization, Sentrx developed several browser-based tools within a highly secure web environment and deployed it in the company's own Safety Response Center. One tool helps manage the workflow of cases. All mailed, faxed or printed paper documents associated with a case are given a barcode, which is scanned each time a step in the process is completed. An electronic case management dashboard displays the status of each team member's assignments and alerts responsible parties of approaching deadlines.

Another tool enables a paperless SAE reporting process. It provides an electronic intake form, query management routines, E2BM transfer to the safety



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**Looking forward**

In a clinical trial, efficacy data is the primary focus of site, sponsor, and CRO personnel. SAEs cannot simply be treated as additional data points, as SUSARs have the potential to stop a trial, render a drug unapprovable or trigger the requirement of a risk management program.

With the pharmaceutical industry committed

to providing access to registries of their clinical trials, SAE data is becoming more visible to the public, press and political entities. Implementing a centralized, time-sensitive process of intake, investigation, integrity and reporting gives drug safety in clinical trials the attention it requires. ■

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database, quality control views, case routing and other features that support Sentrx Safety Monitors in meeting the tight deadlines associated with reporting SUSARs to regulatory agencies. For a paperless environment to be achieved from intake through informing, however, the sponsor and its investigators must be committed to the goal and willing to change their habits.



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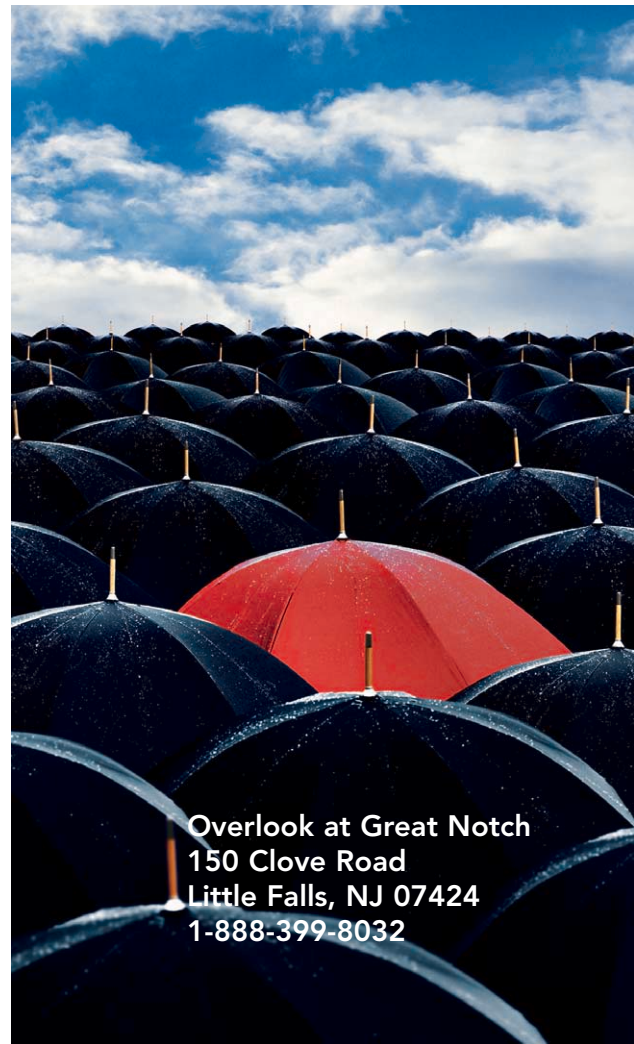
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